10/500,155
File 5:Biosis Previews(R) 1969-2006/Nov W1
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Set Items Description
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Set	Items	Description
S1	93	(HUMAN(W)P53)AND (WILD(W)TYPE) AND ALLELE?
S2	2	S1 AND REVIEW
S3	93	(HUMAN(W)P53) AND (WILD(W)TYPE) AND ALLELE?
S4	0	S3 AND ALLIGN?
S5	0	S3 AND ALIGN?
S6	3	S3 AND COMPARISON?
S7	19	(HUMAN(W)P53)AND (WILD(W)TYPE(W)ALLELE?)

? t s2/7/1-2

2/7/1
DIALOG(R)File 5:Biosis Previews(R)

0015351049 BIOSIS NO.: 200510045549
Generation of loss of heterozygosity and its dependency on p53 status in human lymphoblastoid cells
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JOURNAL: Environmental and Molecular Mutagenesis 45 (2-3): p162-176
MAR-APR05 2005
ISSN: 0893-6692
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Loss of heterozygosity (LOH) is a critical event in the development of human cancers. LOH is thought to result from either a large deletion or recombination between homologous %%%alleles%%% during repair of DNA double-strand breaks (DSBs). These types of genetic alterations produce mutations in the TK gene mutation assay, which detects a wide mutational spectrum, ranging from point mutations to LOH-type mutations. TK6, a human lymphoblastoid cell line, is heterozygous for the thymidine kinase (TK) gene and has a %%%wild%%%-%%%type%%% p53 gene. The related cell lines, TK6-E6 and WTK-1, which are p53-deficient and p53-mutant (Ile237), respectively, are also heterozygous for the TK gene and LOH-type mutation can be detected in these cells. Therefore, comparative studies of TK mutation frequency and spectrum with these cell lines are useful for elucidating the role of p53 in generating LOH and maintaining genomic stability in human cells. We demonstrate here that LOH and its associated genomic instability strongly depend on the p53 status in these cells. TK6-E6 and WTK-1 are defective in the G1/S checkpoint and in apoptosis. Unrepaired DSBs that escape from the checkpoint can potentially initiate genomic instability after DNA replication, resulting in LOH and a variety of chromosome changes. Moreover, genomic instability is enhanced in WTK-1 cells. It is likely that the mutant p53 protein in WTK-1 cells increases LOH in a dominant-negative manner due to its abnormal recombination capacity. We

discuss the mutator phenotype and genomic instability associated with p53 inactivation with the goal of elucidating the mechanisms of mutation and DNA repair in untargeted mutagenesis. Environ. Mol. Mutagen. 45:162-176, 2005. (c) 2005 Wiley-Liss, Inc.

2/7/2
DIALOG(R)File 5:Biosis Previews(R)

0014084804 BIOSIS NO.: 200300042153
Functional analysis of p53 family genes: Potential application to gene therapy.
AUTHOR: Sasaki Yasushi (Reprint); Tokino Takashi (Reprint)
AUTHOR ADDRESS: Department of Molecular Biology, Cancer Research Institute, Sapporo Medical University School of Medicine, Sapporo, Japan**Japan
JOURNAL: Sapporo Medical Journal 71 (1-2): p1-6 April 2002 2002
MEDIUM: print
ISSN: 0036-472X
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: Japanese

ABSTRACT: p53 gene therapy is being tested clinically for the treatment of human cancer, however some cancer models (in vivo and in vitro) are resistant to p53. To explore the potential use of two p53 homologues, p73 and p51/p63, in cancer gene therapy, we introduced p53, p73 and p51/p63 into colorectal cancer cell lines via adenoviral vectors, and compared their effects on cell growth. Among ten cell lines tested, six cell lines displayed a similar response following transduction of p53, p73beta or p51A/p63gamma; two lines underwent cell-cycle arrest, three lines exhibited apoptosis and one line showed no-effect following transduction. The effect on cell-cycle progression was variable in the other four cell lines. Interestingly, three cell lines were resistant to p53-mediated apoptosis, including two lines having endogenous %%%wild%%%-%%%type%%% p53 %%%alleles%%%, but underwent apoptosis after transduction of p73beta or p51A/p63gamma. Similar to p53, transduction of p51A/p63gamma induced extensive apoptosis when combined with adriamycin or X-radiation in SW480 cells, which are normally resistant to apoptosis. Transduction of p73beta and p51A/p63gamma also reduced the tumorigenicity of two colorectal cancer cells in vivo. These results suggest that adenovirus-mediated p73beta and p51A/p63gamma transfer are potential novel approaches for the treatment of human cancers, particularly for tumors that are resistant to p53 gene therapy.

? t s6/7/1-3

6/7/1
DIALOG(R)File 5:Biosis Previews(R)

0014824671 BIOSIS NO.: 200400215428
Loss of p53 transcriptional activity in hepatocellular carcinoma evaluated by yeast-based functional assay: %%%Comparison%%% with p53 immunohistochemistry.
AUTHOR: Mitsumoto Yasuhide (Reprint); Nakajima Tomoki; Marutani Masumi;

Kashiwazaki Haruhiko; Moriguchi Michihisa; Kimura Hiroyuki; Okanoue Takeshi; Kagawa Keizo; Tada Mitsuhiro
AUTHOR ADDRESS: Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kawaramachi-Hirokoji, Kamigyo-Ku, Kyoto, 602-8566, Japan**Japan
JOURNAL: Human Pathology 35 (3): p350-356 March 2004 2004
MEDIUM: print
ISSN: 0046-8177 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We studied the transcriptional activity of p53 protein in 50 tissues of hepatocellular carcinoma (HCC) using a yeast functional assay. In this assay, red yeast colonies indicate that p53 protein cannot bind to its specific domain and has lost its transcriptional activity. We also clarified whether mutant p53 protein could inactivate %%%wild%%%-%%%type%%% p53 protein in a transdominant manner using a modified yeast assay. In addition, we examined whether immunohistochemically detectable p53 protein was functionally inactive. The incidence of p53 inactivation was significantly higher in tumors with capsular invasion. Out of 21 tumors diagnosed with p53 mutations, 11 exhibited >75% red colonies, and all contained missense mutations. In these tumors, p53 function was lost because there was supposedly no intact p53 gene on either %%%allele%%%. One missense mutant produced <60% red colonies, but it was also considered inactive as a p53 protein heterotetramer because of its transdominant activity. In 7 of the remaining 9 tumors, p53 was considered to be mutated on one %%%allele%%% and intact on the other. All of these 7 tumors contained nonsense or frameshift mutations and had no transdominant activity, which suggested that p53 function remained intact. Alternately, immunohistochemical analysis demonstrated that all of the tumors with missense mutations were positively immunostained, whereas those that contained nonsense or frameshift mutations were negatively stained. Consequently, positively immunostaining tumors mostly coincided with p53-inactive tumors. These yeast-based assays suggested that p53 function was retained in some mutant cases. Immunohistochemistry was helpful in screening functionally inactive p53 protein in HCCs.

6/7/2
DIALOG(R)File 5:Biosis Previews(R)

0012910371 BIOSIS NO.: 200100082210
Knock-in mice with a chimeric human/murine p53 gene develop normally and show %%%wild%%%-%%%type%%% p53 responses to DNA damaging agents: A new biomedical research tool
AUTHOR: Luo Jun-Li; Yang Qin; Tong Wei-Min; Hergenhahn Manfred; Wang Zhao-Qi; Hollstein Monica (Reprint)
AUTHOR ADDRESS: Department of Genetic Alterations in Carcinogenesis (C0700), German Cancer Research Center (Deutsches Krebsforschungszentrum), Im Neuenheimer Feld 280, D-69120, Heidelberg, Germany**Germany
JOURNAL: Oncogene 20 (3): p320-328 18 January, 2001 2001
MEDIUM: print
ISSN: 0950-9232
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The high prevalence and great diversity of p53 tumor suppressor gene mutations in human tumors call for development of therapeutic molecules that rescue function of aberrant p53 protein. P53 mutations also offer new approaches to the study of the origins of mutations in human cancer. An experimental mouse model with a genetically modified but normal functioning p53 gene harboring the human rather than the murine core domain, would be of considerable benefit to research on both cancer therapeutics and etiology; however, it is uncertain whether such mice would permit biological functions of p53 to be retained. Using a Cre/lox P gene-targeting approach, we have constructed a %%%human%%% %%%p53%%% knock-in (hupki) mouse strain in which exons 4-9 of the endogenous mouse p53 %%%allele%%% were replaced with the homologous, normal %%%human%%% %%%p53%%% gene sequence. The chimeric p53 %%%allele%%% (p53KI) is properly spliced, transcribed in various tissues at levels equivalent to %%%wild%%%-%%%type%%% mice, and yields cDNA with the anticipated sequence, that is, with a core domain matching that of humans. The hupki p53 protein binds to p53 consensus sequences in gel mobility shift assays and accumulates in the nucleus of hupki fibroblasts in response to UV irradiation, as is characteristic of %%%wild%%%-%%%type%%% p53. Induction of various p53-regulated genes in spleen of gamma-irradiated homozygous hupki mice (p53KI/KI), and the kinetics of p53-dependent apoptosis in thymocytes are similar to results with %%%wild%%%-%%%type%%% (p53+/+) mice, further indicating normal p53 pathway function in the hupki strain. The mice are phenotypically normal and do not develop spontaneous tumors at an early age, in contrast to knock-out (p53-/-) strains with a defective p53 gene. The chimeric (p53KI) %%%allele%%% thus appears to provide a biological equivalent to the endogenous murine (p53+) gene. This strain is a unique tool for examining in vivo spontaneous and induced mutations in %%%human%%% %%%p53%%% gene sequences for %%%comparison%%% with published human tumor p53 mutation spectra. In addition, the hupki strain paves the way for mouse models in pre-clinical testing of pharmaceuticals designed to modulate DNA-binding activity of %%%human%%% %%%p53%%%.

6/7/3
DIALOG(R)File 5:Biosis Previews(R)

0012379498 BIOSIS NO.: 200000097811
Effects of exogenous p53 transduction in thyroid tumor cells with different p53 status
AUTHOR: Moretti F; Nanni S; Farsetti A; Narducci M; Crescenzi M; Giuliacci S; Sacchi A; Pontecorvi A (Reprint)
AUTHOR ADDRESS: Molecular Oncogenesis Laboratory, Regina Elena Cancer Institute and Institute of Medical Pathology, Catholic University, Via delle Messi d'Oro 156, 00158, Rome, Italy**Italy
JOURNAL: Journal of Clinical Endocrinology and Metabolism 85 (1): p302-308 Jan., 2000 2000
MEDIUM: print
ISSN: 0021-972X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recovery of p53 function in undifferentiated thyroid carcinoma cells carrying an altered p53 gene is able to modify cell tumorigenic properties. It is not known whether such an effect may also be achieved in thyroid cancer cells expressing %%%wild%%%-%%%type%%% p53, as in the majority of differentiated thyroid carcinomas. Effects of p53 transduction in a thyroid carcinoma cell line (FRO) exhibiting a %%%wild%%%-%%%type%%% endogenous p53 gene, in %%%comparison%%% to a cell line (WRO) exhibiting mutant p53, were investigated by using an inducible chimeric construct containing %%%human%%% %%%p53%%% complementary DNA fused to the ligand binding domain of the estrogen receptor (p53ER). FRO cells were unaffected by exogenous p53 expression in terms of both proliferation and viability. On the contrary, p53 reexpression in WRO cells containing hemizygous mutated p53 %%%allele%%% caused a strong growth inhibition due to cell accumulation in the G1 phase of the cell cycle. In addition, exogenous p53 did not influence FRO cell behavior in response to TSH treatment or modify cell resistance to the chemotherapeutic agent, doxorubicin. Our results indicate that exogenous expression of %%%wild%%%-%%%type%%% p53 affects thyroid tumorigenic properties only in cells carrying an altered p53, whereas it is ineffective in cells expressing %%%wild%%%-%%%type%%% p53 activity. Therefore, the endogenous p53 status seems to be a major determinant for the effectiveness of a p53-based gene therapy for thyroid cancer.

? t s7/7/1-19

7/7/1
DIALOG(R)File 5:Biosis Previews(R)

0014466183 BIOSIS NO.: 200300434902
Screening of homologous recombination gene polymorphisms in lung cancer patients reveals an association of the NBS1-185Gln variant and p53 gene mutations.
AUTHOR: Medina Pedro P; Ahrendt Steven A; Pollan Marina; Fernandez Paloma; Sidransky David; Sanchez-Cespedes Montserrat (Reprint)
AUTHOR ADDRESS: Molecular Pathology Program, Spanish National Cancer Center, C/ Melchor Fernandez Almagro, 3, 28029, Madrid, Spain**Spain
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JOURNAL: Cancer Epidemiology Biomarkers and Prevention 12 (8): p699-704 August 2003 2003
MEDIUM: print
ISSN: 1055-9965 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Carcinogens present in tobacco smoke lead to several types of DNA damage in bronchial cells. In lung cancer, karyotype, allelotype, and fluorescence in situ hybridization analyses have demonstrated the common presence of aneuploidy, although its severity varies considerably among tumors. Deficiencies in the DNA-double strand break (DSB) repair system may be critical in the generation and persistence of chromosomal gains or losses during lung tumorigenesis. Therefore, we examined whether specific DSB repair gene polymorphisms were associated with an increase in

tobacco-induced DNA damage, including gene mutations (p53 and KRAS) and chromosomal alterations. Nonsynonymous polymorphisms with a frequency higher that 0.1 at the XRCC3, NBS1, and BRCA2 genes were selected for the study. A PCR-RFLP analysis was performed to identify the Met241Thr, Glu185Gln, and Asn372His polymorphisms in the XRCC3, NBS1, and BRCA2 genes, respectively, in 109 lung cancer patients. Interestingly, the prevalence of p53 mutations was significantly greater among individual homozygous for the NBS1-185Gln allele (8 of 8, 100%) than among individuals for the %%%wild%%%-%%%type%%% %%%allele%%% (24 of 52, 46%). This increase in p53 mutation frequency was largely attributable to an increased prevalence of GfwdarwT or CfwdarwA transversions among these patients ($P < 0.001$). In addition, the association between this type of mutation and the NBS1-185Gln allele remained statistically significant after adjusting for age, smoking, and histological cell-type (odds ratio = 3.42 for heterozygous and odds ratio = 38.3 for NBS1-185Gln homozygous). Germ-line variants in the NBS1 gene may play a role in the lung carcinogenesis in cigarette smokers.

7/7/2

0014007513 BIOSIS NO.: 200200601024
Sensitivity of electrospray ionization mass spectrometry detection of codon 249 mutations in the p53 gene compared with RFLP
AUTHOR: Qian Geng-Sun; Kuang Shuang-Yuan; He Xia; Groopman John D (Reprint) ; Jackson Peta E
AUTHOR ADDRESS: Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Baltimore, MD, 21205, USA**USA
JOURNAL: Cancer Epidemiology Biomarkers and Prevention 11 (10 Part 1): p 1126-1129 October, 2002 2002
MEDIUM: print
ISSN: 1055-9965
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Hepatocellular carcinoma (HCC) has several major etiological risk factors, including infection with hepatitis viruses and exposure to aflatoxin B13. A specific missense mutation resulting from a guanine to thymine transversion at the third position of codon 249 in the p53 tumor suppressor gene has been reported in 10-70% of HCCs from areas of high dietary exposure to aflatoxin B1. This mutation has not only been detected in tumor samples but has also been measured in DNA isolated from the blood of patients with HCC in two separate studies by two independent methods: RFLP and short oligonucleotide mass analysis (SOMA), an electrospray ionization mass spectrometry technique. To compare the relative sensitivities of these methodologies, a set of serially diluted samples was analyzed by both techniques. The detection limits of RFLP and SOMA were 6% and 2.4% mutant alleles in the presence of %%%wild%%%-%%%type%%% %%%alleles%%%, respectively. When the DNA samples were predigested with HaeIII before SOMA, the detection limit was improved to 0.4% mutant allele in the presence of %%%wild%%%-%%%type%%% %%%alleles%%% . We have therefore found that SOMA is about 2.5-15-fold more sensitive than RFLP for detection of specific p53 mutations. A set of 26 DNA

samples from HCC and normal liver was analyzed by RFLP and SOMA, and 5 samples were positive for the p53 mutation. An additional 4 samples were found to be positive for the mutation when SOMA was repeated after HaeIII predigestion.

7/7/3
DIALOG(R)File 5:Biosis Previews(R)

0013947037 BIOSIS NO.: 200200540548
Ligation of a primer at a mutation: A method to detect low level mutations in DNA
AUTHOR: Kaur Manjit; Zhang Yuzhi; Liu Wei-Hua; Tetradis Sotirios; Price Brendan D; Makrigiorgos G Mike (Reprint)
AUTHOR ADDRESS: Longwood Radiation Oncology Center, Brigham-Dana Farber Children's Hospitals, 75 Francis Street, Level L2, Radiation Therapy, Boston, MA, 02115, USA**USA
JOURNAL: Mutagenesis 17 (5): p365-373 September, 2002 2002
MEDIUM: print
ISSN: 0267-8357
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Detection of low frequency mutations following exposure to mutagens or during the early stages of cancer development is instrumental for risk assessment and molecular diagnosis. We present a sensitive new method to detect trace levels of DNA mutations induced within a large excess of wild-type sequences. The method is based on mutation-induced generation of new restriction enzyme recognition sites. A DNA sequence is amplified from genomic DNA or cDNA using a high fidelity polymerase. The purified PCR product is digested with a restriction enzyme that recognizes the newly generated restriction site, partially dephosphorylated and ligated with an oligonucleotide at the position of the mutation. The ligated oligonucleotide is then utilized in two rounds of PCR to amplify the mutated DNA but not the %%%wild%%%-%%%type%%% %%%allele%%% that contains no restriction site. An AfwdarwT polymorphism in mRNA (tenascin gene, A2366fwdarwT, AsnfwdarwIle) and a GfwdarwA polymorphism in genomic DNA (Ku gene, G74582fwdarwA, ValfwdarwIle), both of which generate a restriction site for the enzyme SAU3A1, demonstrate the application. Eleven patient samples pre-characterized for the G74582fwdarwA polymorphism in the repair gene Ku are used to demonstrate the reliability of this approach. This technique quantitatively detects the Ku GfwdarwA polymorphism at a mutant frequency of 1.6X10-6 relative to the %%%wild%%%-%%%type%%% %%%allele%%%. Mutations in p53 that are frequently induced by mutagens can readily be detected using the present method. As an example, using a second enzyme BbvI, a mutation frequently encountered in human cancers (G14154fwdarwA mutation, p53 codon 245, ArgfwdarwGln) was detected in patient samples. The process does not require radioactivity, utilizes established procedures and overcomes several factors known to produce false positives in RFLP-based assays. The present amplification via primer ligation at the mutation (APRIL-ATM) has potential applications in the detection of mutagen-generated genetic alterations, early detection of tumor marker mutations in bodily discharges and the diagnosis of minimal residual disease.

7/7/4
DIALOG(R)File 5:Biosis Previews(R)

0013865937 BIOSIS NO.: 200200459448
RT-PCR heteroduplex analysis permits differentiation of transgene and host gene expression in a transgenic animal model
AUTHOR: Duan W; Ding H; Zhu W-G; Srinivasan K; Otterson G A; Villalona-Calero M A (Reprint)
AUTHOR ADDRESS: Arthur G. James Cancer Hospital, Ohio State University, 320 W10th Avenue, B406 Starling-Loving Hall, Columbus, OH, 43210-1240, USA** USA
JOURNAL: BioTechniques 33 (1): p58-66 July, 2002 2002
MEDIUM: print
ISSN: 0736-6205
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In transgenic animal models, the conservation of DNA sequences between the transgene and the host wild-type gene can complicate the evaluation of the expression of each gene. The potential for gene silencing may complicate matters further. Here we report the use of RT-PCR heteroduplex analysis to differentiate the expression of a transgene and its homologous wild-type, even when these genes are very similar in their respective DNA sequences. We designed RT-PCR primers to amplify identically sized 243-bp fragments within the DNA binding domain of the p53 gene from both human and mouse mRNA samples. Ten samples from %%%human%%% %%%p53%%% (273H) transgenic mice and 10 samples from wild-type controls were tested. Heteroduplex bands were formed in all transgenic samples but were absent from all wild-type samples. In addition, RT-PCR heteroduplex analysis was able in one sample to differentiate a silenced transgene from its %%%wild%%%-%%%type%%% %%%allele%%%, without the assistance of sequencing or labeling. In summary, the RT-PCR heteroduplex analysis is easy to use and has the ability to screen a large number of samples in a short time. The RT-PCR heteroduplex analysis is especially useful for the detection of expression when a transgene and the host homologous endogenous allele are too conserved in sequence to design species-specific RT-PCR primers.

7/7/5
DIALOG(R)File 5:Biosis Previews(R)

0013724156 BIOSIS NO.: 200200317667
UV-B-type mutations and chromosomal imbalances indicate common pathways for the development of Merkel and skin squamous cell carcinomas
AUTHOR: Popp Susanne; Waltering Stefan; Herbst Christel; Moll Ingrid; Boukamp Petra (Reprint)
AUTHOR ADDRESS: Division of Genetics of Skin Carcinogenesis, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120, Heidelberg, Germany**Germany
JOURNAL: International Journal of Cancer 99 (3): p352-360 20 May, 2002 2002
MEDIUM: print

ISSN: 0020-7136
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Two developmentally highly divergent nonmelanoma skin cancers, the epidermal squamous cell carcinomas (SCC) and the neuroendocrine Merkel cell carcinomas (MCC), occur late in life at sun-exposed body sites. To determine whether these similarities may indicate common genetic alterations, we studied the genetic profile of 10 MCCs and analyzed 6 derived cell lines and 5 skin SCC lines by comparative genomic hybridization (CGH) and molecular genetic analyses. Although the MCCs were highly divergent-only 3 of the 10 tumors exhibited common gains and losses-they shared gain of 8q21-q22 and loss of 4p15-pter with the genetically much more homogeneous SCC lines. In addition, 2 of 5 SCC and 2 of 6 MCC lines exhibited UV-B-type-specific mutations in the p53 tumor-suppressor gene and a high frequency (9/11) of CCfwdarwTT double base changes in codon 27 of the Harvey (Ha)-ras gene. Since 45% of the tumor lines were homozygous for this nucleotide substitution compared to 14% of the controls and in I MCC patient the %%%wild%%%-%%%type%%% %%%allele%%% was lost in the tumor, this novel polymorphism may contribute to tumor development. On the other hand, loss of 3p, characteristic for SCCs, was rare in MCCs. Although in 2 of 3 SCC lines 3p loss was correlated with reduced expression of the FHIT (fragile histidine triad) gene, the potential tumor suppressor mapped to 3p14.2 and 2 MCC lines with normal 3p showed aberrant or no FHIT transcripts. Taken together, in addition to the common UV-B-specific mutations in the p53 and Ha-ras gene, MCCs and SCCs also share chromosomal imbalances that may point to a common environmental-derived (e.g., UV-A) oxidative damage.

7/7/6
DIALOG(R)File 5:Biosis Previews(R)

0013723102 BIOSIS NO.: 200200316613
Genetic status of cell cycle regulators in squamous cell carcinoma of the oesophagus: The CDKN2A (p16INK4a and p14ARF) and p53 genes are major targets for inactivation
AUTHOR: Smeds Johanna; Berggren Petra; Ma Xin; Xu Zhijian; Hemminki Kari; Kumar Rajiv (Reprint)
AUTHOR ADDRESS: Department of Biosciences, Karolinska Institute, Novum, Huddinge, 141 57, Sweden**Sweden
JOURNAL: Carcinogenesis (Oxford) 23 (4): p645-655 April, 2002 2002
MEDIUM: print
ISSN: 0143-3334
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We determined inactivation of the CDKN2A (p16INk4a and p14ARF) gene in 21 cases of oesophageal squamous cell carcinoma (OSCC). The tumours were also analysed for mutations in exons 5-8 and allelic losses in the p53 gene. In addition, we screened the CDKN2B (p15INK4b), CDKN2C (p18INK4c), CDK4 and p53R2 genes for mutations in the tumour tissues. Besides concomitant alterations in the CDKN2A and p53 loci in more than

half of the cases, our results showed that in 18 OSCC (86%) the CDKN2A (p16INK4a and p14ARF) gene was affected through mutations, homozygous/hemizygous deletions and promoter hypermethylation. Eight out of 10 tumours with mutations or promoter hypermethylation specific to the CDKN2A/p16INK4a gene showed loss of the %%%wild%%%-%%%type%%% %%%allele%%%. One tumour with a single base deletion in the N-terminus (codon 8) of the CDKN2A/p16INK4a gene carried a novel germ-line mutation or a rare polymorphism (Ile51Met) in exon 2 of the CDK4 gene. Promoter hypermethylation in the CDKN2A/p14ARF gene was detected in 11 tumours. In the p53 gene 15 mutations were detected in 14 tumours. We detected an inverse relationship between CDKN2A/p16INK4a inactivation and frequency of loss of heterozygosity at the p53 locus (OR 0.09, 95% CI 0.01-0.98; Fisher exact test, P-value apprx0.03). Screening of nine exons of the p53R2 (Human Genome Organisation (HUGO) official name RRM2B) gene resulted in identification of a novel polymorphism in the 5' untranslated region, which was detected in four cases. Our results suggest that the CDKN2A (p16INK4a and p14ARF) and p53 genes involved in the two cell cycle pathways are major and independent targets of inactivation in OSCC.

7/7/7
DIALOG(R)File 5:Biosis Previews(R)

0013705269 BIOSIS NO.: 200200298780
p53 genotypes and haplotypes associated with lung cancer susceptibility and ethnicity
AUTHOR: Wu Xifeng (Reprint); Zhao Hua; Amos Christopher I; Shete Sanjay; Makan Nimisha; Hong Waun K; Kadlubar Fred F; Spitz Margaret R
AUTHOR ADDRESS: Department of Epidemiology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX, 77030, USA**USA
JOURNAL: Journal of the National Cancer Institute (Bethesda) 94 (9): p 681-690 May 1, 2002 2002
MEDIUM: print
ISSN: 0027-8874
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: The p53 tumor suppressor protein is important in cell-cycle control, apoptosis, and DNA repair. Mutations in p53 have been associated with inherited cancer susceptibility. Because there is a difference in the risk of lung cancer among different ethnic groups, we examined associations between ethnicity and three polymorphisms in p53 (one exonic and two intronic) and haplotypes for the three loci and risk of lung cancer. We also examined the functionality of the p53 variants in apoptosis and DNA repair. Methods: In a case-control study, we frequency matched (by age, sex, and ethnicity) 635 lung cancer case patients and 635 control subjects. p53 genotypes and haplotypes at the three polymorphic sites were determined by restriction fragment length polymorphism analysis of lymphocyte DNA. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between genotype or haplotype and lung cancer risk were determined by logistic regression analysis. Apoptosis and DNA repair capacity were measured in 22 lymphoblastoid cell lines to determine the functional effects of the polymorphisms. All statistical tests were two-sided. Results: Genotype and haplotype frequency distributions were strongly dependent on

ethnicity; variant allele frequencies were highest in African-Americans (29.1%) and lowest in Mexican-Americans (12.2%). Each of the three polymorphisms was associated with an increased risk of lung cancer among all ethnic groups. Moreover, for all three polymorphisms, increased variant allele copy number was associated with increased risk of lung cancer. Similarly, the variant haplotypes were also associated with an increased risk for lung cancer. Lymphoblastoid cell lines with all %%%wild%%%-%%%type%%% %%%alleles%%% at the three loci had statistically significantly higher apoptotic indices (13.66%, 95% CI=8.61% to 18.71%) and DNA repair capacity (27.63%, 95% CI=21.72% to 33.53%) than cell lines with at least one variant allele at all three loci (3.50%, 95% CI=1.08% to 5.91%; and 17.48%, 95% CI=7.99% to 26.96%, respectively). Conclusions: p53 polymorphisms may be associated with increased lung cancer risk and may affect p53 function.

7/7/8
DIALOG(R)File 5:Biosis Previews(R)

0013627926 BIOSIS NO.: 200200221437
Tumour p53 mutations exhibit promoter selective dominance over wild type p53
AUTHOR: Monti Paola; Campomenosi Paola; Ciribilli Yari; Iannone Raffaella; Inga Alberto; Abbondandolo Angelo; Resnick Michael A; Fronza Gilberto (Reprint)
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JOURNAL: Oncogene 21 (11): p1641-1648 7 March, 2002 2002
MEDIUM: print
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The tumour suppressor gene p53 is frequently mutated in human cancer. Tumour derived p53 mutants are usually transcriptionally inactive, but some mutants retain the ability to transactivate a subset of p53 target genes. In addition to simple loss of function, some p53 mutants may be carcinogenic through a dominant negative mechanism. Aiming at a more general classification of p53 mutants into predictive functional categories it is important to determine (i) which p53 mutants are dominant, (ii) what features characterize dominant mutants and (iii) whether dominance is target gene specific. The ability of 71 p53 mutants to inhibit wild type p53 was determined using a simple yeast transcriptional assay. Approximately 30% of the mutants were dominant. They preferentially affect highly conserved amino acids ($P < 0.005$), which are frequently mutated in tumours ($P < 0.005$), and usually located near the DNA binding surface of the protein ($P < 0.001$). Different tumour-derived amino acid substitutions at the same codon usually have the same dominance phenotype. To determine whether the ability of p53 mutants to inhibit wild type p53 is target gene specific, the dominance towards p21, bax, and PIG3 binding sites was examined. Approximately 40% of the 45 mutants examined were dominant for the p21 (17/45) or PIG3 (20/45) responsive elements and 71% (32/45) were dominant for the bax responsive element. These differences are statistically significant (p21 vs bax, $P < 0.003$; bax vs PIG3, $P < 0.02$, Fisher's exact test) and

defined a hierarchy of dominance. Finally, we extended the analysis to a group of mutants isolated in BRCA-associated tumours, some of which retained wild type level of transcription in yeast as well as in human cells, but show gain of function in transformation assays. Since transformation assays require transdominant inhibition of the endogenous %%%wild%%% %%%type%%% %%%allele%%%, one possible explanation for the behaviour of the BRCA-associated mutants is that they adopt conformations able to bind DNA alone but not in mixed tetramers with wild type p53. The yeast data do not support this explanation, because all BRCA-associated mutants that behaved as wild type in transcription assay were recessive in dominance assays.

7/7/9
DIALOG(R)File 5:Biosis Previews(R)

0013413727 BIOSIS NO.: 200200007238
p53 genotypes, haplotypes and lung cancer susceptibility
AUTHOR: Wu Xifeng (Reprint); Zhao Hua (Reprint); Amos Christopher I (Reprint); Shete Sanjay (Reprint); Makan Nimisha (Reprint); Hong Waun K (Reprint); Kadlubar Fred F (Reprint); Spitz Margaret R (Reprint)
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JOURNAL: International Journal of Molecular Medicine 8 (Supplement 1): p S71 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 6th World Congress on Advances in Oncology, and the 4th International Symposium on Molecular Medicine Hersonissos, Crete, Greece October 18-20, 2001; 20011018
ISSN: 1107-3756
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

7/7/10
DIALOG(R)File 5:Biosis Previews(R)

0013251262 BIOSIS NO.: 200100423101
Two metachronous tumors in the radiotherapy fields of a patient with Li-Fraumeni syndrome
AUTHOR: Limacher Jean-Marc (Reprint); Frebourg Thierry; Natarajan-Ame Shanti; Bergerat Jean-Pierre
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JOURNAL: International Journal of Cancer 96 (4): p238-242 20 August, 2001 2001
MEDIUM: print
ISSN: 0020-7136
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A woman with a family history of brain tumors in her daughter and

sister presented with a breast cancer. She subsequently developed two metachronous primary tumors: a small-cell lung cancer and a colon carcinoma. These tumors arose within the internal mammary radiotherapy field and within the field irradiated for ovariolysis. The p53 gene was analyzed in whole blood lymphocytes using a functional assay developed in yeast Saccharomyces cerevisiae, which tests the transcriptional competence of p53. DNA from the colon cancer cells was analyzed by polymerase chain reaction and sequencing. The patient had a germline-inactivating p53 mutation, confirming the diagnosis of Li-Fraumeni syndrome (LFS). The colon tumor and the lung tumor both conserved the mutant p53 allele but had lost the %%%wild%%%-%%%type%%% %%%allele%%%. This observation and the experimental data suggest an abnormal sensitivity of LFS patients to radiogenic carcinogenesis. The indications and extent of radiotherapy in patients with a clinical or molecular diagnosis of LFS should be discussed individually and should take into account the risk of secondary neoplasms arising in the radiation fields.

7/7/11
DIALOG(R)File 5:Biosis Previews(R)

0013248853 BIOSIS NO.: 200100420692
An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma
AUTHOR: Ribeiro Raul C (Reprint); Sandrini Fabiano; Figueiredo Bonald; Zambetti Gerard P; Michalkiewicz Edson; Lafferty Antony R; DeLacerda Luiz ; Rabin Mark; Cadwell Craig; Sampaio Gilberto; Cat Israil; Stratakis Constantine A; Sandrini Romolo
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JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 98 (16): p9330-9335 July 31, 2001 2001
MEDIUM: print
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The incidence of pediatric adrenal cortical carcinoma (ACC) in southern Brazil is 10-15 times higher than that of pediatric ACC worldwide. Because childhood ACC is associated with Li-Fraumeni syndrome, we examined the cancer history and p53 status of 36 Brazilian patients and their families. Remarkably, 35 of 36 patients had an identical germ-line point mutation of p53 encoding an R337H amino acid substitution. Differences within intragenic polymorphic markers demonstrated that at least some mutant alleles arose independently, thus eliminating a founder effect. In tumor cells, the %%%wild%%%-%%%type%%% %%%allele%%% was deleted, and mutant p53 protein accumulated within the nuclei. Although these features are consistent with Li-Fraumeni syndrome-associated adrenal tumors, there was no history of increased cancer incidence among family members. Therefore, this inherited R337H p53 mutation represents a low-penetrance p53 allele that contributes in a tissue-specific manner to the development of pediatric ACC.

7/7/12
DIALOG(R)File 5:Biosis Previews(R)

0013048130 BIOSIS NO.: 200100219969
Visualization of oligonucleotide probes and point mutations in interphase nuclei and DNA fibers using rolling circle DNA amplification
AUTHOR: Zhong Xiao-bo; Lizardi Paul M; Huang Xiao-hua; Bray-Ward Patricia L ; Ward David C (Reprint)
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JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 98 (7): p3940-3945 March 27, 2001 2001
MEDIUM: print
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Rolling circle amplification (RCA) is a surface-anchored DNA replication reaction that can be exploited to visualize single molecular recognition events. Here we report the use of RCA to visualize target DNA sequences as small as 50 nts in peripheral blood lymphocytes or in stretched DNA fibers. Three unique target sequences within the cystic fibrosis transmembrane conductance regulator gene could be detected simultaneously in interphase nuclei, and could be ordered in a linear map in stretched DNA. Allele-discriminating oligonucleoticle probes in conjunction with RCA also were used to discriminate wild-type and mutant alleles in the cystic fibrosis transmembrane conductance regulator, p53, BRCA-1, and Gorlin syndrome genes in the nuclei of cultured cells or in DNA fibers. These observations demonstrate that signal amplification by RCA can be coupled to nucleic acid hybridization and multicolor fluorescence imaging to detect single nucleotide changes in DNA within a cytological context or in single DNA molecules. This provides a means for direct physical haplotyping and the analysis of somatic mutations on a cell-by-cell basis.

7/7/13
DIALOG(R)File 5:Biosis Previews(R)

0012865967 BIOSIS NO.: 200100037806
p53 intronic point mutation, aberrant splicing and telomeric associations in a case of B-chronic lymphocytic leukaemia
AUTHOR: Bromidge Teresa (Reprint); Lowe Christopher; Prentice Archie; Johnson Stephen
AUTHOR ADDRESS: Leukaemia Research Unit, Department of Haematology, Musgrove Park Hospital, Taunton, Somerset, TA1 5DA, UK**UK
JOURNAL: British Journal of Haematology 111 (1): p223-229 October, 2000 2000
MEDIUM: print
ISSN: 0007-1048
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We report a case of chronic lymphocytic leukaemia (CLL) with telomeric associations and a p53 intronic point mutation. Karyotypic analysis revealed clonal and non-clonal telomeric associations, accompanied by clonal cytogenetic abnormalities and also in isolation. The p53 mutation, which occurred at the invariant base pair -2 of the splice acceptor site in intron 7 resulted in the abolition of correct splicing of exon 7 to exon 8. Multiple aberrant splice products were characterized, all of which differed from wildtype in the DNA binding domain. Fluorescence in situ hybridization demonstrated that the clone retained two copies of the p53 gene and wild-type p53 transcript was detected on cloning of reverse transcriptase polymerase chain reaction (RT-PCR) product, indicating that one %%%wild%%%-%%%type%%% %%%allele%%% remained. However, a plasmid clone with correct splicing at the exon 7/8 boundary, but with a 21 bp deletion in exon 8, was also found at low frequency. This finding indicates clonal evolution, resulting in complete loss of wild-type p53. The intronic point mutation was not present in DNA extracted from cervical tissue indicating that it was a leukaemic phenomenon. This is the first case of an intronic point mutation to be reported in CLL. This mutation led to chaotic p53 expression and, interestingly, occurred in a case showing telomeric associations, a rare phenomenon in B-CLL.

0012815480 BIOSIS NO.: 200000533793
Reduced latency but no increased brain tumor penetrance in mice with astrocyte specific expression of a %%%human%%% %%%p53%%% mutant
AUTHOR: Klein Michael A; Ruedi Daniela; Nozaki Michimasa; Dell Elizabeth W; Diserens Annie-Claire; Seelentag Walter; Janzer Robert C; Aguzzi Adriano; Hegi Monika E (Reprint)
AUTHOR ADDRESS: Laboratory of Tumor Biology and Genetics, Department of Neurosurgery, CHUV BH19-110, 1011, Lausanne, Switzerland**Switzerland
JOURNAL: Oncogene 19 (47): p5329-5337 9 November, 2000 2000
MEDIUM: print
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: p53-germline mutations located in the core DNA-binding domain have been associated with a more dominant tumor penetrance especially for breast cancer and brain tumors. We previously reported an unusual accumulation of CNS tumors associated with a unique p53 germline mutation, Y236DELTA (deletion of codon 236). To test whether this tissue-specific tumor predisposition reflects a gain-of-function activity of Y236DELTA, we generated transgenic mice expressing Y236DELTA in astrocytes using the regulatory elements of the glial fibrillary acidic protein (GFAP) gene. After transplacental exposure to N-ethyl-N-nitrosourea (25 mg/kg BW) brain tumors developed in 18% (7/39) of GFAP-Y236DELTA transgenic p53+/- mice, while in p53+/- mice the incidence was 28% (11/40) (P>0.3). However, the mean tumor latency for GFAP-Y236DELTA/p53+/- mice was significantly shorter than for p53+/- mice, with 19.9 weeks vs 31.6 weeks (P=0.039), respectively. Taken together, cell specific expression of Y236DELTA results in an

acceleration of tumor progression but does not confer a higher tumor • penetrance. Conceivably, the transdominant effect of Y236DELTA provided a growth advantage early in the progression of neoplastic cells, since the endogenous p53 %%%wild%%%-%%%type%%% %%%allele%%% was lost in all brain tumors independent of the genotype. This reflects well observations from human astrocytic neoplasms with p53 mutations.

7/7/15
DIALOG(R)File 5:Biosis Previews(R)

0012709138 BIOSIS NO.: 200000427451
Genetic polymorphisms of CYP2D6, CYP1A1, GSTM1 and p53 genes in a unique Siberian population of Tundra Nentsi
AUTHOR: Duzhak T (Reprint); Mitrofanov D; Ostashevskii V; Gutkina N; Chasovnikova O; Posukh O; Osipova L; Lyakhovich V V
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JOURNAL: Pharmacogenetics 10 (6): p531-537 August, 2000 2000
MEDIUM: print
ISSN: 0960-314X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The purpose of this study was to establish the frequencies of CYP2D6, CYP1A1, GSTM1 and p53 polymorphic genotypes in Tundra Nentsi, which comprises the small group of indigenous people belonging to Northern Mongoloids and Caucasians of Western Siberia. A total number of 102 Tundra Nentsi individuals and 96 Caucasians of Western Siberia were genotyped by means of polymerase chain reaction-based assays. Mutated alleles comprising CYP2D6*4, CYP1A1Val, GSTM1*0 and p53Pro were analysed along with the %%%wild%%%-%%%type%%% %%%alleles%%%. The results showed the intermedial position of CYP2D6*4 allele frequency in Tundra Nentsi, compared to Caucasians and Orientals (0.07 versus 0.2, P = 0.0003; 0.07 versus 0.003, P = 1 X 10-6, respectively). Thus, our data indicate that the intermedial position of Tundra Nentsi between Orientals and Caucasians most likely shows the Caucasian ancestral origin of CYP2D6*4 allele. Comparative analysis of p53Pro allele frequency showed the pronounced ethnic differences with geographic gradient. Though the frequency of p53Pro allele ranged from 0.17 in Tundra Nentsi up to 0.3 in Caucasians of Western Siberia (P = 0.002), which is in agreement with the previously reported radial distribution of the known genetic markers. No differences were found in the CYP1A1Val allele distribution among Caucasians of Western Siberia and Caucasoid populations presented in other studies, whereas the frequency of Val allele in Nentsi was 1.5-fold higher (P = 0.076) compared to the Japanese group. It was found that the frequency of GSTM1 null genotype in Tundra Nentsi was only 39.8%. The frequency of GSTM1 null genotype in females was higher than in males (0.27 and 0.50, respectively) but that difference was not statistically significant. Comparative analyses of the distribution of putative markers towards cancer susceptibility, CYP1A1Val, GSTM1*0 and p53Pro alleles, have shown that the healthy Tundra Nentsi population (Northern Mongoloids) have a low number of p53Pro alleles and GSTM1*0/*0 genotypes and a high level of CYP1A1Val alleles. Further investigations of gene polymorphisms in isolated Northern native populations would be valuable

in clarifying the origin of Northern natives. All this is important for comparative analyses of pharmacogenetic data in Mongoloid populations.

7/7/16
DIALOG(R)File 5:Biosis Previews(R)

0012587243 BIOSIS NO.: 200000305556
Mutation of p53 with loss of heterozygosity in the osteosarcomatous component of a dedifferentiated chondrosarcoma
AUTHOR: Grote H J; Schneider-Stock Regine; Neumann W; Roessner A (Reprint)
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JOURNAL: Virchows Archiv 436 (5): p494-497 May, 2000 2000
MEDIUM: print
ISSN: 0945-6317
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We investigated a dedifferentiated chondrosarcoma of a 61-year-old woman with an osteosarcomatous high-grade component for p53 alteration. The low-grade cartilaginous and the high-grade osteosarcomatous components of the tumor were macrodissected and evaluated separately by immunohistochemistry and molecular biology. We used PCR-SSCP analysis and direct sequencing to screen exons 4-8 for p53 mutations. The p53 intron 1-polymorphism was investigated for loss of heterozygosity. A functionally relevant p53 missense mutation in codon 193 of exon 6 (A-to-T transversion) with loss of %%%wild%%%-%%%type%%% %%%allele%%% was detected only in the dedifferentiated component. Using the monoclonal antibody DO-1, immunohistochemistry failed to show p53 overexpression. This evidence of p53 mutation may be regarded as at least a co-factor that "switched" the preexisting low-grade conventional chondrosarcoma to a highly malignant dedifferentiated tumor.

7/7/17
DIALOG(R)File 5:Biosis Previews(R)

0012341641 BIOSIS NO.: 200000059954
Enrichment of mutant alleles by chromatographic removal of %%%wild%%% %%%type%%% %%%alleles%%%: A new principle for the detection of alleles with unknown point mutations at excess of %%%wild%%% %%%type%%% %%%alleles%%%
AUTHOR: Nollau Peter (Reprint); Fischer Carsten (Reprint); Tschentscher Peter (Reprint); Wagener Christoph (Reprint)
AUTHOR ADDRESS: Abteilung fuer Klinische Chemie, Medizinische Klinik, Universitaetskrankenhaus Eppendorf, Hamburg, Germany**Germany
JOURNAL: Clinical Chemistry and Laboratory Medicine 37 (9): p877-881 Sept., 1999 1999
MEDIUM: print
ISSN: 1434-6621
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In human carcinomas, mutations that alter tumour genes such as the KRAS, P53, or APC genes, are mostly point mutations. The detection of mutant alleles of tumour genes in specimens such as urine, pancreatic juice, sputum, and stool holds great promise for an early diagnosis of cancer. In addition, the detection of mutant tumour genes in tissue samples, such as lymph nodes or resection margins, may allow a sensitive diagnosis of residual malignant disease. However, the reliable detection of mutant alleles in excess of %%%wild%%% %%%type%%% %%%alleles%%% remains an unresolved analytical problem when the mutations are not known a priori. In the present communication, a new approach is described which makes possible the detection of unknown point mutations in tumour genes at excess of %%%wild%%% %%%type%%% %%%alleles%%%. The method is based on the removal of %%%wild%%% %%%type%%% %%%alleles%%% by hybridisation to immobilised complementary oligonucleotides. Using this approach, an enrichment of mutant KRAS, P53 and APC alleles of one mutant in up to 103 normal alleles has been achieved. Parallel miniaturised separation units with oligonucleotides complementary to defined sequences of a %%%wild%%% %%%type%%% %%%allele%%% should allow the detection of unknown point mutations as well as small insertions or deletions which occur in the sequence range covered by the oligonucleotides.

0009706198 BIOSIS NO.: 199598174031
The Canine p53 Gene is Subject to Somatic Mutations in Thyroid Carcinoma
AUTHOR: Devilee Peter (Reprint); Van Leeuwen Irma S; Viesten Annet; Rutteman Gerard R; Vos Jan H; Cornelisse Cees J
AUTHOR ADDRESS: Dep. Human Genetics, Wassenaarseweg 72, 2333 Al Leiden, Netherlands**Netherlands
JOURNAL: Anticancer Research 14 (5A): p2039-2046 1994 1994
ISSN: 0250-7005
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In many different types of tumors in man and mouse, p53 is the tumor suppressor gene most frequently affected by a combination of somatic mutation and loss of the %%%wild%%%-%%%type%%% %%%allele%%%. In order to develop a molecular tool to study the genetic evolution of tumors in the dog, we have cloned an evolutionary conserved part of the canine homologue of p53. The isolated genomic segment, 534 bp in length, contains the 3' half of exon 5, the complete exon 6 and the 5' half of exon 7, as well as the intronic intervening sequences. The gene organization of this segment shows strong homolog to that published earlier for a number of other species, including man, mouse, and Xenopus laevis. This conservation is apparent at the DNA sequence level, as well as at the deduced amino acid sequence level. mRNA expression can be detected at low levels in normal tissues with increased mitotic activity, and in the Madin-Darby canine kidney cell line. A fwdarw G T transversion was found in 1 out of 23 investigated primary thyroid carcinomas at a position corresponding to codon 174 in the %%%human%%% %%%p53%%%, and was predicted to give rise to an amino acid substitution in the protein. These results suggest that p53 plays a role in the development of

malignancy in the dog, in a way comparable to that in man.

7/7/19
DIALOG(R)File 5:Biosis Previews(R)

0008223723 BIOSIS NO.: 199293066614
SUPPRESSION OF ACUTE LYMPHOBLASTIC LEUKEMIA BY THE HUMAN WILD-TYPE P53 GENE
AUTHOR: CHENG J (Reprint); YEE J-K; YEARGIN J; FRIEDMANN T; HAAS M
AUTHOR ADDRESS: DEP BIOLOGY, UNIVERSITY CALIFORNIA, SAN DIEGO, 9500 GILMAN DRIVE, LA JOLLA, CALIF 92093-0063, USA**USA
JOURNAL: Cancer Research 52 (1): p222-226 1992
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Independent mutations in both alleles of the p53 tumor suppressor gene are a frequent finding in human T-cell acute lymphoblastic leukemia (T-ALL) cell lines and in the cells of some T-ALL patients in relapse. One major goal of studying the status of p53 (and other tumor suppressor genes) in human cancer is to facilitate the suppression of the tumorigenic phenotype through the restoration of the expression of the %%%wild%%%-%%%type%%% %%%allele%%%. While the efficient insertion of a suppressor into all cells of solid/metastatic human tumors may at present be impossible, insertion into leukemia cells may be feasible due to the accessibility of the leukemia cells in the body. To examine the feasibility of suppressing the tumorigenicity of human T-leukemia cells, the human T-ALL cell line Be-13, which lacks endogenous p53 protein, was infected with a recombinant retrovirus encoding the %%%wild%%%-%%%type%%% %%%allele%%% of %%%human%%% %%%p53%%% (hwtp53). Expression of p53 reduced the growth rate of infected Be-13 cells in vitro, suppressed colony formation in methylcellulose cultures, and abrogated their tumorigenic phenotype in nude mice in vivo. These results suggest that suppression of the leukemic phenotype of relapse T-ALL-derived Be-13 cells is feasible. Acute leukemia cell suppression via high-efficiency infection with retroviruses encoding wtp53 may be feasible and beneficial in T-ALL cases as part of a bone marrow transplantation regimen in an effort to reduce the frequency of posttransplantation relapse.
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